REMARKS

Applicants appreciate the notification that claims 23-25 are allowed over the prior art and that claims 4-8 and 26-33 would be allowable if rewritten as independent claims.

Applicants have added new claim 48, which specifies that "the presence of the verification oligonucleotide on the sensing interface causes an increase in the insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium." This claim is supported throughout the specification. See, for example, page 14, lines 6-8, where it is explained that detection of the target is expected to "introduce a electron transfer resistance." No new matter has been added.

Rejections Under 35 U.S.C. §112, second paragraph (written description)

The Examiner rejected claims 26-33 as indefinite. Applicants have amended claim 26 to recite a "quartz crystal microbalance probe" Such devices are well-known in the art, see, e.g., page 6, lines 1-5 of the specification. In view of this amendment, Applicants request that this rejection of claim 26-33 be withdrawn.

Rejections Under 35 U.S.C. §102(e)

Blackburn et al.

The examiner previously rejected claims 1 and 2 as anticipated by Blackburn et al. (U.S. Patent No. 6,686,150; "Blackburn"). In the advisory action the examiner maintained this rejection arguing that Blackburn teaches measuring insulation of the sensing interface (i.e., surface of the electrode) to interfacial electron transfer between the sensing interface and the surrounding medium (i.e., the hybridization buffer containing ETM)".

As explained previously, the methods of Blackburn employ an oligonucleotide that has bound to it, e.g., via a covalent bond, to a electron transfer moiety (ETM) such as ferrocene. This is shown below in a portion of Fig. 30 from Blackburn.

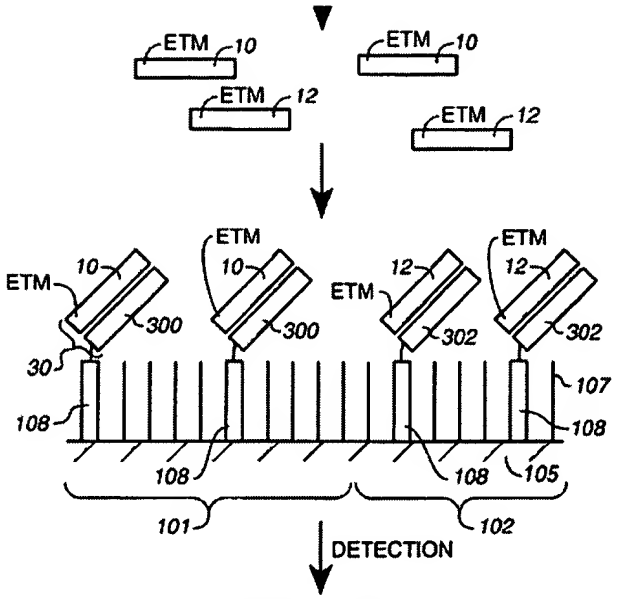
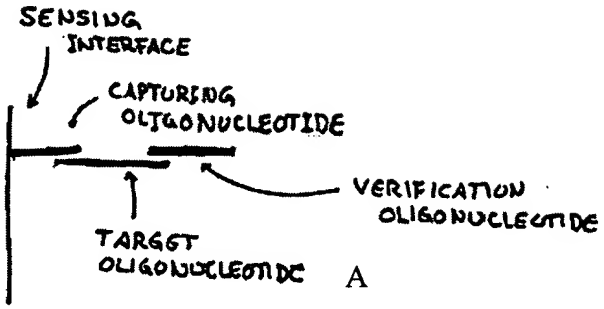


FIG._30

The oligonucleotide is detected by measuring electron transfer between the ETM, which is bound to an oligonucleotide, and the electrode – not between the surrounding medium and the electrode as suggested by the examiner. Detection of the oligonucleotide occurs because the ETM is brought into proximity to the electrode.

This stands in sharp contrast to the presently claimed methods. Where the presence of a particular oligonucleotide on a sensing interface is detected "by measuring insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium". Thus, the presence of a particular oligonucleotide, here the "verification oligonucleotide" is detected because the presence of the oligonucleotide leads to insulation of the sensing surface from electron transfer between the surface and the surrounding medium. The detection does not arise as it does in Blackburn from bringing an electron transfer moiety in proximity to the electrode. The sketches below, which depict aspects of one embodiment of the invention, help to illustrate this point.

When the target oligonucleotide has hybridized to both the capturing oligonulceotide and the verification oligonulceotide they are arranged on the sensing interface as depicted below.



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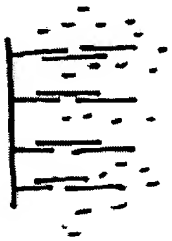
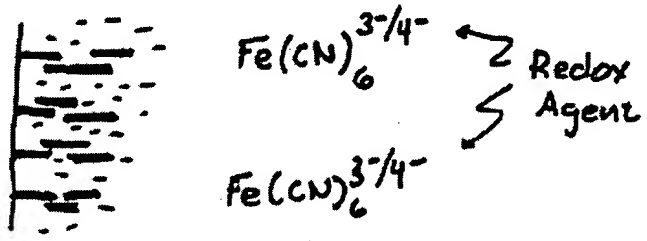
Of course, there are actually many such hybridizations taking place on the sensing interface as depicted below. Since oligonucleotides are negatively charged (shown by the numerous "-" in the sketch below), the binding of the target oligonucleotide and the verification oligonucleotide greatly increase the density of negative charge near the sensing interface effectively creating an insulating shield.



This increase in negative charge near the sensing interface brought about by the presence of the target oligonucleotide insulates the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium, which can contain a redox agent such as $Fe(CN)_6^{3-/4-}$ as shown below and as described in the present application.



Thus, the presently method is not dependent, as is Blackburn, on bringing an ETM into proximity to an electrode. Instead it relies on insulation of the sensing interface.

The presently claimed method can also include a verification moiety that includes a recognition agent which can specifically bind to a signal-amplifying agent (see claim 4). The signal amplifying agent can, for example, convert a substrate to a product that is deposited on the sensing interface. This deposition of material can physically insulate the sensing surface effectively adding to the insulating effect of the oligonucleotides themselves.

In view of the forgoing, applicants respectfully request that the rejections under 35 U.S.C. §102(e) based on Blackburn be withdrawn.

Applicants have added new claim 48 which requires that "the presence of the verification oligonucleotide on the sensing interface causes an increase in the insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium." This claim clearly distinguishes the method from that of Blackburn et al. Applicants submit that this new claim should not be rejected as anticipated by Blackburn et al.

Durst et al.

The examiner rejected claims 23-26, 28, 29 and 31 as anticipated by Durst et al. (U.S. Patent No. 6,358,752; "Durst").

The examiner argues that Durst discloses a device which meets the limitations of the current claims because a capturing oligonucleotide, a "first binding material" in the terminology of Durst, is carried on an absorbent material, which the examiner insists is a "sensing interface" within the meaning of the present claims. Applicants disagree. The absorbent material of Durst is not a sensing interface.

In arguing that the absorbent material of Durst is a sensing interface, the examiner makes much of the fact that an interface is a surface that forms a boundary of two, for example, phases. However, examiner focus on the term "interface" is misplaced. In the present claims the capturing oligonucleotide is bound to the "sensing interface" (emphasis added). The examiner has improperly ignored the sensing limitation in the phase "sensing interface". The absorbent material of Durst cannot be viewed as a sensing surface. The absorbent material does no

sensing. Instead, the absorbent material is merely a support for the first binding material. In Durst it is the electrodes, which Durst explains, can be above or below the absorbent material, that performs a sensing function. It is the electrodes and not the absorbent material that receive the signal that indicates whether the analyte is present or not. Thus, Durst does not disclose a device in which an oligonucleotide is bound to a sensing interface. Accordingly, Durst cannot anticipate any of claims 23-26, 28, 29 and 31.

In addition, Applicants have amended claim 23 to specify that the presence of the signal-amplifying agent on the sensing interface is detected by "monitoring electron transfer resistance of the sensing interface". Even if the absorbent material of Durst could be considered a sensing interface, which it cannot, there is nothing in Durst that suggests monitoring the electron transfer resistance of the absorbent material. For this independent reason, Durst cannot anticipate any of claims 23-26, 28, 29 and 31.

In view of the forgoing, applicants respectfully request that the rejections under 35 U.S.C. §102(e) based on Durst be withdrawn.

Rejections Under 35 U.S.C. §103

The examiner rejected claim 3 as obvious in view of Blackburn taken with Lizardi et al. (U.S. Patent 6,143,495). According to the examiner, it would have been obvious to modify the method of Blackburn to use probes of the size described by Lizardi et al. Claim 3 depends from claim 1. As noted above, Blackburn does not disclose a method that includes "measuring insulation of the sensing interface to interfacial electron transfer between the sensing interface and the surrounding medium (emphasis added)" as required by claims 1 and 3. Lizardi et al. does not suggest such a method. Thus, Blackburn and Lizardi et al., no matter how combined, cannot render claim 3 obvious.

In view of the forgoing, applicants respectfully request that the rejections under 35 U.S.C. §103 be withdrawn

Enclosed is a Petition for Extension of Time fee with the appropriate fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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